**NAME: FAKROGHA LATRICIA OYINTARE**

**LEVEL:300**

**MATRIC NO:17/MHS01/132**

A REVIEW ON THE DEVELOPMENTAL GENETICS OF CEREBELLUM

The cerebellum originates from the alar plate of the neural tube, which gives rise to the sensory structures of the brain. Functionally, the cerebellum joins the sensory and motor systems and is essential for coordinating communications between these two systems. The cerebellar cortex is a **trilaminar** structure and each mature layer contains a deﬁned set of cell types:

* the outermost molecular layer: contains stellate and basket interneurons, in addition to glial cells;
* the Purkinje cell layer, located beneath the molecular layer, contains the cell bodies of the eponymous neuron (PURKINJE), Bergmann glia and candelabrum cells
* the granule layer, located immediately beneath the Purkinje layer, which contains granule cells, golgi cells, unipolar brush cells, and a few other minor cell types

The current understanding of cerebellar development has largely been derived from gene expression, lineage tracing, and genetic perturbation studies in the mouse, whose cerebellar anatomy closely resemble those in humans. During development, the cerebellar territory is established through the signaling actions of the isthmic organizer (IO). The IO sets up the boundary between the mesencephalic and metencephalic vesicles around embryonic day (E) 8.5–9 in the mouse. The morphogen Otx2 is expressed rostral to the IO in the mesencephalic vesicles and speciﬁes the midbrain territory. Caudal to the IO, the metencephalic vesicle is marked by Gbx2 expression, and Gbx2 is required for the development of cerebellum. At the isthmus, restricted expression of secreted factors, such as fibroblast growth factor 8, *FGF8* and *Wnt1*, the mammalian homolog of *Drosophila* wingless gene, as well as homeobox proteins *En1* and *En2* and paired box genes *Pax2* and *Pax5* are required for early specification of midbrain and hindbrain structures

The cerebellum has major cell types which consist of **glutamatergic, GABAergic, and glial cells**. Glutamatergic, excitatory cell types consist of granule, unipolar brush cell, and deep cerebellar nuclear neurons, whereas Purkinje cells, interneurons, and a contingent of deep cerebellar nuclear neurons are GABAergic, inhibitory cells. Each cell type has a complex migratory pattern and occupy defined positions in the mature cerebellum that are linked to its birth order from the germinal zones of the cerebellar anlage(primordium).

The cerebellar anlage arises from the rhombencephalic vesicle of the neural tube. Cerebellar cell types arise from two anatomically and molecularly nonoverlapping germinal zones: The Ventricular zone and Rhombic lip.

**VENTRICULAR ZONE AND GABAERGIC LINEAGES(NEURONS)**

The ventricular zone is located in the roof of the fourth ventricle and is characterized by expression of **Ptf1a**, a basic helix-loop-helix (BHLH) transcription factor. All cerebellar GABAergic lineages, including the GABAergic nuclear neurons, Purkinje cells, and interneurons are formed in the **VENTRICULAR** zone. Other gene expressions that have been observed in this zone is Ascl1 (or Mash1), Ngn1, Ngn2, Cyclin D2, Zac1. These genes divide the ventricular zone into two distinct molecular compartments: a rostral domain of Ngn1- /Ngn2+ /Ascl1+ and a ventral domain of Ngn1+ /Ngn2+ /Ascl1+. Through lineage tracing, it has been discovered that Ngn1+ cells give rise to Purkinje cells and inhibitory interneurons while NG2+ cells become small GABAergic nuclear neurons and Purkinje cells. Cyclin D2 is essential for GABAergic stellate cells. Zac1 is a gene expression for GABAergic nuclear neurons.

**RHOMBIC LIP AND GLUTAMATERGIC LINEAGES(NEURONS)**

The rhombic lip is located in the rostral edge of the neural tube surrounding the fourth ventricle. The rhombic lip germinal zone is deﬁned by the expression of **Atoh1(Math1)**, also a BHLH transcription factor. Rhombic lip cells give rise to the cerebellar glutamatergic lineages, consisting of the large glutamatergic nuclear neurons, granular cells, and unipolar brush cells. Other expressions found in this zone are Pax6, Lmx1a and Tbr2. Pax6 is expressed in the precursors of glutamatergic nuclear neurons, granule cells, and unipolar brush cells and plays crucial roles in the development of these rhombic lip lineages. Tbr2 is expressed in and specific for unipolar brush cells.

**CEREBELLAR GLIAL CELLS**

The cerebellum consists of four major types of glial cells –astrocytes, Bergmann glia (a major subtype of astrocytes), oligodendrocytes, and microglia. Using cell lineage studies and zone markers or gene expressions, Atoh1 and Ptfa1, it was observed that cerebellar glial cells originated from the ventricular zone. Other studies showed that that some cells that emigrated from the ventricular zone remained mitotically active in the overlying cerebellar parenchyma during late embryonic and neonatal period and a proposal was made that the cerebellar parenchyma is a secondary germinal zone that gives rise to cerebellar glial cells.

2. GENETIC BASES OF CEREBELLAR DISORDERS

A. **JOUBERT SYNDROME**

 Joubert syndrome is an inherited congenital cerebellar ataxia that is characterized by an unusual midbrain–hindbrain malformation, the molar tooth sign. It has to do with the dysfunction of a subcellular organelle, the primary cilium Interestingly, primary cilia are determinant for sonic hedgehog signal transduction. Disruption of primary cilia formation blocks the proliferation of neural progenitors of granule cells mediated by sonic hedgehog

**GENETIC BASES**

 Joubert syndrome is associated with mutations of genes encoding components of the primary cilia, 21 causative mutant genes have been identified with autosomal or X-linked recessive inheritance. To mention a few, INPP5E, AHI1, ARL13B, CCD2A, CEP290,NPHP1,RPGRIP1L and TMEM67 etc. Mutations in CC2D2A and RPGRIP1L includes the disorder, COACH (cerebellar vermis hypoplasia, oligophrenia, ataxia, coloboma and hepatic fibrosis).

B. **DANDY-WALKER MALFORMATION**

This disorder affects the development of the brain, mostly the cerebellum.

**GENETIC BASES**

The disorder is caused by the mutation of some specific genes. They are ZIC1, ZIC4 and FOXC1. The developmental process affected is granule cell differentiation.

C. **CEREBELLAR VERMIS HYPOPLASIA**

This is associated with a normal position of the cerebellar vermis relative to the brainstem or minimal upward rotation due to a mildly enlarged fourth ventricle, without elevation of the tentorium.

**GENETIC BASES**

The implicated human gene here is the OPHNI gene. The developmental process affected is spine morphogenesis.

D. **PONTOCEREBELLAR HYPOPLASIA**

Pontocerebellar hypoplasia is characterized by hypoplasia of the brainstem and cerebellum at birth. It can also be neurodegenerative.

**GENETIC BASES**

 The implicated human genes are *CASK*, *RARS2*, *TSEN54*, *TSEN34*, and *TSEN2*. The developmental processes affected are spine development, cell proliferation, tRNA splicing and cellular maintenance.

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